Applicant respectfully submits that no new matter has been added by way of this amendment.

I. Rejections under 35 U.S.C. § 112, second paragraph

Claims 6-21 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. These rejections are respectfully traversed. Claims 6-10, 12-16, 18 and 20 have been amended to point out more particularly and claim more distinctly the subject matter of the claimed invention.

The Office's rejections under 35 U.S.C. § 112, second paragraph, and Applicant's response are as follows:

a) In claim 7, the term "the profile shown in FIG.1(c)": claim 7 has been amended to point out more particularly the subject matter of the claimed invention.

b) In claim 8, the term "relatively constant": claim 8 has been amended to point out more particularly the subject matter of the claimed invention.

c) In claims 9-10, 12 and 16-17, the term "increased": claims 9-10, 12 and 16-17 have been amended to point out more particularly the subject matter of the claimed invention.

d) In claims 13-15 and 18-19, the term "improved": claims 13-15 and 18-19 have been amended to point out more particularly the subject matter of the claimed invention.

e) In claims 6-10, 12-13, 15-16, 18 and 20, the term "the application": claims 6-10, 12-13, 15-16, 18 and 20 have been amended to point out more particularly the subject matter of the claimed invention. Specifically, the claims have been amended to reference "the method" instead of "the application."

f) In claims 6-7, the term "steady-state": Applicant submits that the term "steady-state" is not a relative term that renders the claims indefinite, as argued by the Office, but is a term of art easily understood by those ordinarily skilled in the art. For example, steady state can be described as the condition that exists when the rate of infusion of a drug or compound is equal to the rate of elimination of the drug or compound. *See, e.g.,* Remingtons at page 1134.

f) In claim 21, the term "normal range": Applicant submits that the term "normal range" is not a relative term but is a definitive term that one ordinarily skilled in the art would understand to mean the range found in a normal individual or individuals.

Thus, in view of the above, Applicant submits that claims 6-21 are definite and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

II. Rejections under 35 U.S.C. § 103

Claims 1-21, 27, 53-55, 57-58, 60-64 and 79-145 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mak *et al.* (WO 99/24041-A1) and Heiber, *et al.* (WO 93/25168), and Omar (U.S. Patent No. 5,730,987) and Moreland *et al.* (Life Sciences 1998, 62(2), 309-318) in view of Allen (WO 96/27372-A1). The Office Action stated that:

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular steroid, testosterone, C1-C4 alcohol, and the particular penetration enhancer, C8-C22 fatty acid and isopropyl myristate in a method for improving the efficacy of the composition herein useful for treating erectile dysfunction in a male who may be an eugonadal, and to further add the phosphodiesterase type 5 inhibitor, sildenafil or yohimbine HCl to the composition, and optimize the effective amounts of active ingredients in the composition.

This rejection is respectfully traversed.

It is well established that the burden of establishing a *prima facie* case of obviousness lies with the Examiner. In determining obviousness, one must focus on the invention as a whole. *See* In re Keuhl, 475 F.2d 658, 177 U.S.P.Q. 250 (C.C.P.A 1973); Symbol Technologies Inc. v. Opticon Inc., 19 USPQ 2d 1241, 1246 (Fed. Cir. 1991). Thus, "[i]n determining the difference between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves have been obvious, but whether the claimed invention as a whole would have been obvious. *See* MPEP 2141.02 (emphasis in original). Thus, patentability of a method of use claim hinges on the patentability of the underlying composition, and even if the steps recited in the methods are well known, so long as the

method uses a patentable material, it is unobvious. *See* In re Pleuddemann, 910 F.2d 283, 15 U.S.P.Q.2d 1782 (Fed. Cir. 1990).

In view of the amendments and remarks presented herein, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. As taught by the present invention, in one aspect, Applicant claims a method of transdermally delivering testosterone to a male subject in need thereof, comprising administering a pharmacologically effective amount of a composition consisting essentially of:

a) about 0.5 % to about 10 % testosterone;

b) about 30 % to about 98 % alcohol selected from the group consisting of ethanol, and isopropanol;

c) about 0.1 % to about 5 % isopropyl myristate;

d) about 1 % to about 5 % sodium hydroxide; and

e) about 0.1 % to about 5 % gelling agent.

In rejecting the present claimed invention under 35 U.S.C. § 103, the Office Action stated that:

> Since all composition components herein are known to be useful to treat male erectile dysfunction, it is considered *prima facie* obvious to combine them into a single composition useful for the very same purpose.

(emphasis added). As stated above, however, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. In this case, the present claimed method utilizes a novel and nonobvious composition that is subject to a notice of allowance in the parent case, U.S. Patent Application serial No. 09/651,777 ("the '777 application"). Therefore, the basis for this obviousness rejection does not take into consideration the claimed invention as a whole, but looks only at the components themselves. Additionally, Applicant acknowledges that the Office Action stated that:

> The prior art does not expressly disclose a method of improving the efficacy of a pharmaceutical useful for treating erectile dysfunction in a male who may be an eugonadal comprising the particular steroid, testosterone, C_1-C_4 alcohol, and the particular penetration enhancer, isopropyl myristate, and the effective amounts of active ingredient in the composition.

Applicant therefore contends that the 35 U.S.C. § 103(a) rejection of the present claims is improper.

Applicant also contends that the use of In re Kerkhoven, 626 F.2d 846 (CCPA 1980), in supporting the rejection of the present claims is misplaced. In re Kerkhoven holds that:

> It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose.

Id. at 850 (emphasis added). As acknowledged in the parent case, the '777 application, the novel and unobvious composition as claimed in the present case is not taught by the prior art. "Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." MPEP 2141.02 (emphasis added). Thus, the present invention taken as a whole cannot be combined without using hindsight because the novel and unobvious composition of the present invention was not taught by the prior art.

In the references cited by the Examiner, Omar teaches oral administration of a powdered composition of lyophilized roe and powdered extract of *Ginkgo biloba*. It also mentions that testosterone may be administered by injection, orally or by buccal tablets for hypogonadism. However, Omar does not teach or suggest the present invention of improving the efficacy of a pharmaceutical administered to a male subject useful for treating erectile dysfunction by percutaneously administering the present claimed composition.

Mak *et al.* teach transdermal and topical delivery of testosterone, a C1-C4 alcohol and a penetration-enhancing agent. Mak *et al.* also do not teach or suggest a method of

improving the efficacy of a pharmaceutical administered to a male subject useful for treating erectile dysfunction by percutaneously administering the present claimed composition.

Heiber *et al.* teach the use of varying amounts of glycerin in a composition containing testosterone, a C2 or C3 alcohol, for example, ethanol, glycerol monoleate, and methyl laureate, useful in methods of moderating and maintaining transdermal drug delivery to the derma/mucosa at a relatively sustained rate over the duration of the application to either an application or afflicted situs. Heiber *et al.* do not teach or suggest a method of improving the efficacy of a pharmaceutical administered to a male subject useful for treating erectile dysfunction by percutaneously administering the present claimed composition.

Moreland *et al.* teach oral administration of sildenafil for the treatment of male erectile dysfunction. Moreland *et al.* also do not teach or suggest improving the efficacy of a pharmaceutical administered to a male subject useful for treating erectile dysfunction by percutaneously administering the present claimed composition.

Allen teaches a water-based topical cream containing the vasodilator nitroglycerin (which is not a hormone that plays a role in erections) for the treatment of male erectile dysfunction. Allen does not teach or suggest improving the efficacy of a pharmaceutical administered to a male subject useful for treating erectile dysfunction by percutaneously administering the present claimed composition.

In the 35 U.S.C. §103(a) rejection of the present claims, the Office Action has cited no pertinent reference showing or suggesting to one of ordinary skill in the art the present invention as a whole. Reconsideration and withdrawal of this 35 U.S.C. § 103(a) rejection is respectfully requested.

III. Rejections under the Judicially-Created Doctrine of Obviousness-Type Double Patenting

a) Rejection of claims 1-21, 27, 53-55, 57-58, 60-64 and 79-145 over claims 18-42 of U.S. Patent No. 6,503,894

The Office rejected claims 1-21, 27, 53-55, 57-58, 60-64 and 79-145 for obviousness-type double patenting in view of claims 18-42 of U.S. Patent No. 6,503,894. This rejection is respectfully traversed.

The present application is a divisional of 09/651,777, filed on August 30, 2000, now U.S. Patent No. 6,503,894. The present application was filed in response to a restriction requirement made during the prosecution of the '777 application.

M.P.E.P. 804 states: "a double patenting rejection is not permitted where the claimed subject matter is presented in a divisional application as a result of a restriction requirement made in a parent application under 35 U.S.C. 121." As such, the rejection of claims 1-21, 27, 53-55, 57-58, 60-64 and 79-145 for obviousness-type double patenting in view of claims 18-42 of U.S. Patent No. 6,503,894 is improper and must be withdrawn.

b) Provisional rejection of claims 1-21, 27, 53-55, 57-58, 60-64 and 79-145 over claims 33, 35-36, 41-42, 45, 48-49, 57-59, 62, 64, 75-83, 88-93, 97-99, and 101-210 of co-pending Application No. 09/703,753

The Office provisionally rejected claims 1-21, 27, 53-55, 57-58, 60-64 and 79-145 for obviousness-type double patenting in view of claims 33, 35-36, 41-42, 45, 48-49, 57-59, 62, 64, 75-83, 88-93, 97-99, and 101-210 of co-pending U.S. Application No. 09/703,753 (the '753 application). This rejection is respectfully traversed.

Claims 33, 35-36, 41-42, 45, 48-49, 57-59, 62, 64, 75-83, 88-93, 97-99, and 101-210 of the '753 application are generally directed to a method for improving the efficacy of a pharmaceutical useful for treating erectile dysfunction in a male subject, comprising percutaneously administering to an area of skin of the subject a pharmacologically effective amount of a testosterone composition. Claims 33, 35-36, 41-42, 45, 48-49, 57-59, 62, 64, 75-

83, 88-93, 97-99, and 101-210 of the '753 application do not claim or suggest methods of transdermally delivering testosterone to a male subject comprising administering a pharmacologically effective amount of a testosterone composition to the skin of the subject.

Applicant, on the other hand, claims methods of transdermally delivering testosterone to a male subject comprising administering a pharmacologically effective amount of a testosterone composition to the skin of the male subject. Because the claims of the '753 application do not teach or suggest the subject matter of Applicant's claims, the obviousness-type double patenting rejection is improper and withdrawal of this rejection is respectfully requested.

To establish obviousness-type double patenting, the Office must show that the claimed inventions are not patentably distinct and are based on a *prima facie* showing of obviousness. *In re Vogel*, 422 F.2d 438, 441, 164 U.S.P.Q. 619, 621-622 (C.C.P.A. 1970). The Office must present clear evidence to establish why the variation would be obvious. *In re Kaplan,* 789 F.2d 1574, 1578, 229 U.S.P.Q. 678, 682 (Fed. Cir. 1986); *Ex parte Davis*, 56 U.S.P.Q.2d 1434, 1437-1438 (Bd. Pat. App. Int. 2000) (unpublished). The Office may not use the disclosure of the patent or patent application upon which the rejection is based as prior art. *In re Aldrich,* 398 F.2d 855, 859, 158 U.S.P.Q. 311, 313-314 (C.C.P.A. 1968). Furthermore, the Office must compare the properly interpreted claims as a whole. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1278, 23 U.S.P.Q.2d 1839, 1843 (Fed. Cir. 1992).

Applicant respectfully submits that the Office has not shown that the claimed inventions are not patentably distinct and has not presented a *prima facie* case of obviousness-type double patenting. The Office has not presented any evidence to establish why the variation would be obvious, and has merely made broad, sweeping statements as to obviousness. As such, the Office has not shown that the claims of the '753 application

teaches or suggests the subject matter of Applicant's claims, and withdrawal of the provisional rejection of the claims for obviousness-type double patenting in view of claims 33, 35-36, 41-42, 45, 48-49, 57-59, 62, 64, 75-83, 88-93, 97-99, and 101-210 of co-pending U.S. Application No. 09/703,753 is respectfully requested.

CONCLUSION

With entry of the above Amendment and in view of the foregoing remarks, it is respectfully submitted that claims 1-21, 27, 53-55, 57-58, 60-64 and 79-157 are in condition for allowance.

None of Applicant's amendments or cancellations are to be construed as dedicating any such subject matter to the public, and Applicant reserves all rights to pursue any such subject matter in this or a related patent application. The amendments are made solely to expedite prosecution.

Submitted below is separate page titled "Version with Marking to Show Changes Made to the Claims" showing a marked-up copy of prior pending claims and a copy of the "Pending Claims as of May 12, 2003."

It is respectfully submitted in view of the foregoing Amendment and Remarks that all of the objections and rejections in the Office Action dated January 10, 2003, have been overcome and should be withdrawn. Applicants respectfully request early and favorable notification to that effect.

The Examiner is invited to call Applicant's undersigned attorney at (312) 701-8979 for questions and to expedite prosecution.

Respectfully submitted,

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Version with Marking to Show Changes Made to the Claims

6. (Amended) The method of claim 1, wherein the [application] method results in a steady-state testosterone 24-hour pharmacokinetics profile in the male subject, wherein the profile exhibits a first testosterone serum concentration upon administration of the composition and exhibits a second testosterone serum concentration having a small increase compared to the first testosterone serum concentration at about two hours after application, followed by a decrease to a third testosterone serum concentration that remains relatively constant for the remainder of the day.

7. (Amended) The method of claim 6, wherein the [application results in a steady-state testosterone 24-hour pharmacokinetics profile approximating the profile shown in Fig. 1(c)] first testosterone serum concentration is between about 400 ng/dL to about 900 ng/dL, the second testosterone serum concentration is between about 500 ng/dL to about 1000 ng/dL , and the third testosterone serum concentration is between about 450 ng/dL to about 950 ng/dL.

8. (Amended) The method of claim 6, wherein the [relatively constant] third testosterone serum concentration is between about 300 ng/dL and about 1,000 ng/dL.

9. (Amended) The method of claim 1, wherein the [application] method causes an increased average dihydrotestosterone serum concentration in the male subject compared to the average dihydrotestosterone serum concentration of the male subject before administration of the composition.

10. (Amended) The method of claim 1, wherein the [application] method causes an increase in the bone mineral density of the male subject compared to the bone mineral density of the male subject before administration of the composition.

12. (Amended) The method of claim 1, wherein the [application] method causes increased libido in the male subject compared to the libido of the male subject before administration of the composition.

13. (Amended) The method of claim 1, wherein the [application] method causes improved sexual performance in the male subject compared to the sexual performance of the male subject before administration of the composition.

14. (Amended) The method of claim 13, wherein the improved sexual performance comprises an increase in the percentage of full erection by the male subject compared to the percentage of full erection by the male subject before administration of the composition.

15. (Amended) The method of claim 1, wherein the [application] method causes improved mood in the male subject compared to the mood of the male subject before administration of the composition.

16. (Amended) The method of claim 1, wherein the [application] method causes increased muscle strength in the male subject compared to the muscle strength of the male subject before administration of the composition.

18. (Amended) The method of claim 1, wherein the [application] method causes improved body composition in the male subject compared to the body composition of the male subject before administration of the composition.

20. (Amended) The method of claim 1, wherein the [application] method causes negligible skin irritation.

146. (New) A method of transdermally delivering testosterone to a male subject in need thereof, comprising administering to the subject a pharmacologically effective amount of a composition to a selected area of skin of the subject, wherein the composition comprises: testosterone, at least one penetration enhancer and at least one gelling agent; and wherein the testosterone is absorbed into the bloodstream of the subject at a rate and duration that maintains a circulating serum concentration of the testosterone greater than about 400 ng testosterone per dl serum during a time period beginning about 2 hours after administration and ending about 24 hours after administration; and wherein the method results in a steady-state testosterone 24-hour pharmacokinetics profile in the male subject, wherein the profile exhibits a first testosterone serum concentration upon administration of the composition and exhibits a second testosterone serum concentration having a small increase at about two hours after application compared to the first testosterone serum concentration, followed by a decrease to a third testosterone serum concentration that remains relatively constant for the remainder of the day.

147. (New) The method of claim 146, wherein the first testosterone serum concentration is between about 400 ng/dL to about 900 ng/dL, the second testosterone serum concentration is between about 500 ng/dL to about 1000 ng/dL , and the third testosterone serum concentration is between about 450 ng/dL to about 950 ng/dL.

148. (New) The method of claim 146, wherein the first testosterone serum concentration is between about 400 ng/dL to about 1000 ng/dL, the second testosterone serum concentration is between about 400 ng/dL to about 1000 ng/dL , and the third testosterone serum concentration is between about 400 ng/dL to about 1000 ng/dL.

149. (New) The method of claim 146, wherein the first testosterone serum concentration is between about 450 ng/dL to about 900 ng/dL, the second testosterone serum

concentration is between about 550 ng/dL to about 1000 ng/dL , and the third testosterone serum concentration is between about 450 ng/dL to about 1000 ng/dL.

150. (New) The method of claim 146, wherein the second testosterone serum concentration is from about 1 to about 2 times the first testosterone serum concentration.

151. (New) The method of claim 146, wherein the third testosterone serum concentration is within about 200 ng/dL of the first testosterone serum concentration.